Observation: the variety of views on what might comprise the 3DVC framework and how 3DVCs might be used to advance science seemed to equal or exceed the number of attendees.

Opinion: after a few years of successful operation, the space of envisioned uses will not shrink. It will have expanded and include uses not expressed or even envisioned at the workshop. The same holds true for the list of stakeholders: 3DVC will be successful because the user community is expanding.

Opinion: users will come to the 3DVC operation to explore answers to how, why, and what if questions. They will do so by conducting experiments in silico. Few questions will require use of fully detailed in silico cells, because the questions posed will focus on a subset of cell capabilities and selected aspects of cell behaviors.

Opinion: to increase stakeholder participation, it will be necessary to progressively facilitate flexibility and increase the variety of how, why, and what if questions that can be productively explored, even in the face of considerable uncertainty. That can be done most easily if the "cells" that are needed for any one experiment can be plugged together using components drawn from the frameworks expanding inventory, where each has attached its own use and validation record. I would expect stakeholders to often find one or more existing components inadequate for their goals and so they iteratively refine and improve available components adding and validating new knowledge until objectives are met. Enabling doing so will be essential. All of that will be done within the 3DVC framework and copies of the new, improved (fully documented) components will be added to the component inventory within the 3DVC framework for others to use (or not).

Frameworks now in use in other domains facilitate activities such as those above, and that provides feasibility evidence. Ptolemy II is an example, but it cannot be adapted directly for 3DVC use because it was not designed for biomedical research use cases. http://ptolemy.eecs.berkeley.edu/ptolemyII/

Opinion: after the 3DVC operation passes its first major milestone, I envision access being increased each year. Core use may be restricted to the current set of research scientists and graduate students who have used online training to demonstrate competencies. I envision additional circles of access designed for in silico experiments that have larger education and training objectives. In 15-20 years, maybe sooner, one circle may be available to teams of grade school students and their teachers. Advanced counterparts to Bill Swartout's virtual museum guides would facilitate their access and "manage" their 3DVC experience.
http://ict.usc.edu/prototypes/museum-guides/
http://ict.usc.edu/news/icts-bill-swartout-wins-major-ai-award/
These "lab assistants" would assist the grade school team to design, set-up, and run their mammalian-cell-focused in silico experiments. The "lab assistant" would assemble "cells" appropriate for their experiments by using an automatically

generated requirements statement to select from the available inventory of component. The lab assistants could even conduct the experiments and provide and describe the results, or guide the students to do it themselves, even allowing "mistakes" to occur (which of course the assistant would later point out and explain). The lab assistant could also show where, how, and why the results are uncertain because of gaps in current knowledge. A record of those experiments would remain within the framework for other to visit or even extend.

Tasks within the framework that can be automated, those used by the "lab assistant," for example, including some that are technically complicated and demanding, such as recording in silico observations, statistical analyses, setting up an experiment, parameter sweeps, cross-model validation, etc., can be conducted automatically, "behind the scenes" using advanced versions of today's software actor models.
http://en.wikipedia.org/wiki/Actor_model

After 15-20 years, the component inventory may include 500 or more mammalian mitochondria analogs that have survived several rounds of validation and testing. Together they will represent most of what we think we know about mammalian mitochondria. However, each mitochondrion analog will be just a "model" suitable for use within those 3DVC experiments having overlapping (mitochondria) use case-based requirements. For other scenarios, they may be "wrong" or have not yet undergone validation. The framework will automatically generate requirements and later specifications for particular 3DVC experiments following a dialog with the scientist-stakeholder.

Some of the above mammalian mitochondria may be maximally fine-grin (and have more extensive execution requirements [memory, CPUs, etc.]) for well-validated mechanisms. Others may be hybrids that use a variety of validated rules as placeholders for details. Still others may be completely rule-based and suitable for uses where mitochondria functions will not fundamentally change during the experiments. Others may be placeholders for all or some of the mitochondria in one 3DVC, etc. Some may be suitable for visualization, others not. Etc.

If a coarse-grain (e.g., rule-based) mitochondrion is in use and the scientist decides to conduct a different experiment requiring molecular-level interventions, then the framework can assist the scientist in selecting a suitable, replacement analog and automatically parameterize it for current behaviors (from the previous experiments) using cross-model validation methods. It would unplug the current mitochondria analogs from current 3DVCs and plug in the "new" mitochondria without compromising any of the other already validated cell components or behaviors.

A framework such as that envisioned will be feasible by making all component groundings[1], within and between cells, and from in silico to wet-lab, explicit and

separate from in silico mechanisms for all components across all levels of granularity.

After 15-20 years, once the 3DVC operation makes operational the above capabilities, the biological and scientific landscape will be radically altered. It will be SOP for scientists to conduct many in silico experiments in advance of relatively expensive wet-lab experiments. Whereas today only about 1 in 10 of the wet-lab experiments that are actually initiated are productive, e.g., in terms of providing new knowledge or being publishable. The envisioned 3DVC operation will enable improving that ratio to 1 in 5 or even better: by so doing the pace of scientific advancement will increase. At that stage, in silico and wet-lab experimentation will be inextricably intertwined.

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[1] See the following for a definition and discussion of groundings and their consequences in multiscale computational models.
http://www.tbiomed.com/content/8/1/35/abstract